Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 42-60 are pending in the application, with claims 42 and 52 being the independent claims. Claim 61 is sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 42, 52, and 54 are sought to be amended. Support for the amendments to claims 42 and 54 can be found at page 8, line 4. The amendment to claim 54 is solely to correct an obvious typographical error. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Applicants acknowledge that claims 48 and 57 are withdrawn from consideration as a result of the Species Election filed on June 8, 2007. However, despite the Examiner's indication to the contrary, claims 50 and 59 should not be withdrawn from consideration because these claims read on the elected species SEQ ID NO: 3. Accordingly, Applicants request that the Examiner correct this error and consider claims 50 and 59 as currently pending in the application.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. Summary of the Office Action

In the Office Action dated December 11, 2007, the Examiner has withdrawn the objection to the title, the objections to the specification, the rejection under 35 U.S.C. §

112, second paragraph, the rejection under 35 U.S.C. § 112, first paragraph, for enablement, and the rejection under 35 U.S.C. § 102(b) over Barske *et al.* (WO 03/018631). The Examiner has maintained three rejections and added a new rejection.

III. Rejection under 35 U.S.C. § 112, First Paragraph, is Traversed

In section 6 of the Office Action at pages 3-10, claims 42-47, 49, 51-56, 58, and 60 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to meet the written description requirement. Applicants respectfully disagree. However, in an effort to facilitate prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claims 42 and 52 to specify that the soluble Nogo receptor-1 polypeptide "comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain."

Applicants submit that the present specification provides sufficient written description to convey to one of ordinary skill that Applicants had possession of the claims as currently presented. According to the Examiner, however, "a soluble Nogo receptor-1 polypeptide does not provide ample written description for the compounds since the claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention." Office Action at page 5. Applicants respectfully disagree. First, the claims require administering a therapeutically effective amount of a *soluble* Nogo receptor-1 polypeptide. The specification as filed clearly defines a *soluble* Nogo receptor-1 polypeptide as a Nogo receptor-1 polypeptide that "lack[s] a signal sequence and a functional GPI anchor (*i.e.*, no GPI anchor or a GPI anchor that fails to efficiently associate to a cell membrane)." Specification at page 8, lines 4-6. Second, the claims

specify that the soluble Nogo receptor-1 polypeptide comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain. Thus, with reference to the specification, Applicants respectfully assert that one of skill in the art could readily determine the structural features of and what compounds qualify as a soluble Nogo receptor-1 polypeptide, wherein said soluble Nogo receptor-1 polypeptide comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain.

The Examiner also asserts that "though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples." Office Action at page 5. Applicants respectfully disagree. As indicated above, the claims require a soluble Nogo receptor-1 polypeptide, wherein said soluble Nogo receptor-1 polypeptide comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain. Furthermore, the specification provides the amino acid sequences of soluble Nogo receptor-1 polypeptides of the invention, *see* SEQ ID NOs: 3-6, and detailed structure-function studies in the Examples, *see id.* at page 18, line 1, through page 20, line 14. For example, as clearly demonstrated in Example 3, binding of the soluble Nogo receptor-1 polypeptides to Aβ peptides "requires the entire LRR region." *See id.* at page 20, lines 7-8. Thus, Applicants respectfully submit that the specification provides sufficient correlation between the structure and function of soluble Nogo receptor-1 polypeptides as claimed.

The Examiner has also asserted that:

> claim 42 is broad[ly] generic[, and] the possible structural variations are limitless to any class of peptide or a peptide-like molecule that make up the class of Nogo receptor-1 polypeptide. . . . Moreover, the specification

> lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives.

Office Action at pages 5-6. Applicants disagree and respectfully submit that the specification describes a number of representative examples of the claimed genus of soluble Nogo receptor-1 polypeptides, wherein said soluble Nogo receptor-1 polypeptide comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain. *See, e.g.*, specification at page 7, line 16, through page 9, line 9. Further, as indicated previously in the Amendment and Reply Under 37 C.F.R. § 1.111 filed October 10, 2007, an Applicant is not required to disclose or provide a working example of every species of a given genus in order to meet the written description requirement of 35 U.S.C. § 112. *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. Int. 1994).

The Examiner, however, appears to misconstrue the claim language directed to a *soluble* Nogo receptor-1 polypeptide, and the clear teachings of the specification, to include other polypeptides and molecules that should not be encompassed by the currently pending claims 42-46, 49, 51-55, 58, and 60. For example, the Examiner states that:

> [t]he specification disclosed that "Nogo receptor antagonist" means a molecule that inhibits the binding of Nogo receptor-1 to a ligand (e.g., NogoA, NogoB, NogoC, MAG, OM-gp) (see paragraph [0026]). Further, the specification discloses that Nogo receptor antagonist may include soluble Nogo receptor-1 polypeptides, antibodies that bind to the Nogo receptor protein and antigen-binding fragments of such antibodies, and small molecule antagonists (see paragraph [0030]).

Office Action at page 6. Thus, the Examiner appears to equate any Nogo receptor antagonist with a soluble Nogo receptor-1 polypeptide, which is not correct.

First, Applicants would like to clarify that although the specification does state that "Nogo receptor-1 is also variously referred to as 'Nogo receptor,' 'NogoR,' 'NogoR-

1,' 'NgR,' and 'NgR-1,'" *id.* at page 7, lines 18-19, and defines a Nogo receptor polypeptide to "include[] both full-length Nogo receptor-1 protein and fragments thereof that bind Aβ peptide or antagonize Nogo receptor function," *id.* page 6, lines 20-22, the specification as filed clearly distinguishes a *soluble* Nogo receptor-1 polypeptide from a Nogo receptor-1 polypeptide. Furthermore, as stated below, the genus of soluble Nogo receptor-1 polypeptides would not include all Nogo receptor-1 polypeptides because the latter includes the full-length protein.

Next, it appears to Applicants that the Examiner is erroneously including, *inter alia*, antibodies and small molecule antagonists within the genus of soluble Nogo receptor-1 polypeptides, in contrast to the clear teachings of the specification. Applicants would like to clear up any confusion and emphasize that the genus of *soluble* Nogo receptor-1 *polypeptides* is narrower than the Examiner's characterization. *See, e.g.*, specification at page 7, line 16, through page 8, line 11.

The genus of soluble Nogo receptor-1 polypeptides does not include antibodies that bind to the Nogo receptor protein and antigen-binding fragments of such antibodies or small molecule antagonists. These embodiments are encompassed by the broader genus "Nogo receptor antagonists," which includes the genus of soluble Nogo receptor-1 polypeptides but is of different scope than the soluble Nogo receptor-1 polypeptides genus, as clearly defined in the specification. *See id.* at page 7, lines 10-14. Therefore, Applicants respectfully assert that the inclusion of antibodies and small molecule antagonists in the genus of "soluble Nogo receptor-1 polypeptides" is improper and irrelevant to the determination of whether one skilled in the art could reasonably conclude that the inventors have possession of soluble Nogo receptor-1 polypeptides in

the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02.

Nor does the genus of *soluble* Nogo receptor-1 polypeptides include the full-length Nogo receptor-1. The specification specifically describes a soluble Nogo receptor-1 polypeptide, *see* specification at page 8, lines 3-6, and very clearly delineates the differences from the full-length Nogo receptor-1, *i.e.*, the latter has a signal sequence and a functional GPI anchor. *Compra id.* at page 7, lines 19-22, *with* page 8, lines 4-6. These differences also apply to other full-length Nogo receptors. For example, the Examiner has asserted that the genus of soluble Nogo receptor-1 polypeptides includes GenBank Accession Nos. Q86UN2 and NP_075358. *See* Office Action at page 7. Neither of these sequences would function as a *soluble* Nogo receptor-1 polypeptide as claimed because, *inter alia*, these sequences are not soluble as required by the claims, *i.e.*, they contain GPI anchors, and thus, sites of attachment to cellular membranes. *See* Fankhauser and Mäser, Bioinformatics 21: 1846-52 (2005). Therefore, the Applicants believe that the specification as filed, clearly describes and distinguishes a soluble Nogo receptor-1 polypeptide from full-length Nogo receptors.

Finally, by misconstruing a soluble Nogo receptor-1 polypeptide, the Examiner has contemplated species of polypeptides that were not described as falling within the genus of soluble Nogo receptor-1 polypeptides. For example, the Examiner asserts that peptides disclosed in PCT/US02/32007, which "have the amino acid sequence depicted in SEQ ID NO: 8, 10, 12, 14, 16, 18 and 20 (all 25 amino acid residues) (see p. 20, lines 6-12)," would fall within the genus of soluble Nogo receptor-1 polypeptides. Office Action at page 9. As a result, the Examiner has concluded that so construed, the

specification "lack[s] sufficient variety of species [because] the specification does not provide any examples of derivatives." Office Action at page 6.

Applicants respectfully disagree and submit that the specification describes a number of representative examples of the presently claimed genus of soluble Nogo receptor-1 polypeptides that comprise an NT domain, eight leucine-rich repeats, and an LRRCT domain, including derivatives. *See* specification at page 7, line 16, through page 9, line 9. Contrary to the Examiner's assertions, the specification does "describe any analogs and homologs of [soluble] Nogo receptor-1 polypeptide . . . [sufficiently] to encompass the derivatives." Office Action at page 7. As indicated in the Amendment and Reply Under 37 C.F.R. § 1.111 filed October 10, 2007, the soluble Nogo receptor-1 polypeptides of the invention include, for example, SEQ ID NOs: 3-6, as well as additional polypeptides disclosed in International Patent Applications PCT/US02/32007 and PCT/US03/25004. Specification at page 8, lines 4-11. Further, the soluble Nogo receptor-1 polypeptides of the invention do not include the peptides disclosed in PCT/US02/32007 because, *inter alia*, the peptides do not comprise an NT domain, 8 LRRs, and an LRRCT domain.

Moreover, one of skill in the art would know that derivatives are readily defined, including derivatives of SEQ ID NOs: 3-6 with up to ten conservative amino acid substitutions. For example, as clearly demonstrated in Example 2 of the specification as filed, the interaction of Aβ-AP peptide is specific for NgR1 and not NgR2 or NgR3, despite shared sequence similarities. *Id.* at page 19, lines 11-13. By comparing the sequences of NgR1, NgR2, and NgR3 and using at a minimum this sequence comparison as a guide, one skilled in the art could reasonably conclude that up to ten conservative

amino acid substitutions do not encompass "innumerable possibilities." Office Action at page 7. Therefore, Applicants believe that the above response, including the clarification of the genus of soluble Nogo receptor-1 polypeptides of the invention and a representative number of species, sufficiently demonstrates the possession of the claimed invention at the time of application.

Despite the fact, as indicated above, that Applicants have clearly shown a sufficient correlation between structure and function with regard to soluble Nogo receptor-1 polypeptides, Applicants respectfully submit that the Examiner's requirement that Applicants provide a correlation between the structure and function of the claimed polypeptides and to provide examples of derivatives, is not applicable to the current state of written description law. According to the Federal Circuit in *Capon v. Eshhar,* 418 F.3d 1349, 1358 (Fed Cir. 2005), the written description requirement must be viewed in light of the state of the art at the time of filing. Applicants submit that, when viewed in light of the state of the art at the time of filing the present application, the specification fully supports the presently claimed invention.

Capon clarifies the written description requirement as delineated by *Fiers v. Revel,* 984 F.2d 1164 (Fed. Cir. 1993), *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 927 F.2d 1200 (Fed. Cir. 1991) and *Eli Lilly.* In discussing the current state of the written description requirement under 35 U.S.C. § 112, first paragraph, the Federal Circuit stated, "[t]he 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the *same way.* As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." *Id.* at 1358 (emphasis added). The

invention claimed in *Capon* involved the combination of known DNA sequences, an antigen-binding domain and lymphocyte-receptor-protein, into a chimeric molecule that could be used to induce signaling events in the target cells. The court indicated that when the "invention does not concern the discovery of gene function or structure, as in *Lilly*[, in other words, the genes] are prepared from *known* DNA sequences of *known* function[, a] requirement that these sequences must be analyzed and reported in the specification *does not add descriptive substance*." *Id.* at 1358 (emphasis added).

As in *Capon*, the presently claimed invention does not concern the discovery of gene or protein function or structure. Just as the chimeric DNA molecules in *Capon* were known DNA sequences, the soluble Nogo receptor-1 polypeptides utilized in the present invention are *known* proteins.[1] Describing every soluble Nogo receptor-1 polypeptide that can be used in the practice of the present invention would not add descriptive substance to the present application, and hence is not required under *Capon*. *Id.*

Applicants respectfully submit that the presently claimed invention is directed to a method for reducing the levels of Aβ peptide or treating a disease, disorder, or condition associated with plaques of Aβ peptide by administering a soluble Nogo receptor-1 polypeptide, *not* to an unknown genus of proteins. As noted in *Capon*, when the prior art includes the relevant information, "precedent does not set a *per se* rule that the information must be determined afresh." *Capon,* 418 F.3d at 1358. Because Applicants are not claiming unknown proteins but rather a method of using soluble Nogo

[1] As described in reply to the art rejections below, while the proteins were known, it was not known or obvious that soluble Nogo receptor-1 polypeptides are useful for reducing the levels of Aβ peptide or treating a disease, disorder or condition associated with plaques of Aβ peptide.

receptor-1 polypeptides, they are not required to disclose every soluble Nogo receptor-1 polypeptide that can be used in the practice of the present invention. The ordinarily skilled artisan would readily envision soluble Nogo receptor-1 polypeptide useful in the practice of the present invention. Specifically, the Examiner is directed to the present specification at page 8, line 4, through page 9, line 9, where several soluble Nogo receptor-1 polypeptides are described, including SEQ ID NOs: 3-6.

The description of these various soluble Nogo receptor-1 polypeptides for use in the practice of the present invention satisfies the holding of *Lilly*, as clarified by *Capon*, and provides sufficient written description such that the ordinarily skilled artisan would determine that the inventors, at the time the application was filed, had full possession of the claimed invention. *See also, Invitrogen Corp. v. Clontech Lab., Inc.*, 429 F.3d 1052, 1073 (Fed. Cir. 2005) (holding that description of a single species is sufficient written description for claims directed to a modified polypeptide having DNA polymerase activity).

Hence, Applicants respectfully assert that, even without the Federal Circuit's clarification of the written description law in *Capon*, the present specification provides sufficient written description to convey to one of ordinary skill that Applicants had possession of the full scope of the soluble Nogo receptor-1 polypeptides of the invention upon filing of the application. In light of *Capon*, Applicants respectfully assert that the present specification satisfies the clarified standard because the soluble Nogo receptor-1 polypeptides utilized in the present invention are *known* proteins. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

IV. Rejections under 35 U.S.C. § 102 are Traversed

A. The Rejection over Baker et al. (U.S. Pat. No. 7,029,874) under 35 U.S.C. § 102(e)

In section 17 of the Office Action at pages 10-12, claims 42, 47, 49, and 58 were rejected as allegedly being anticipated under 35 U.S.C. § 102(e) by Baker *et al.* (U.S. Pat. No. 7,029,874) (hereinafter "Baker"). Applicants respectfully traverse this rejection.

Under 35 U.S.C. §102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). As presented, claim 42 (and thus claims depending therefrom) is drawn to a method for reducing the levels of Aβ peptide in a mammalian brain, comprising administering a therapeutically effective amount of a soluble Nogo receptor-1 polypeptide, wherein said soluble Nogo receptor-1 polypeptide comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain. These methods are not disclosed by Baker.

Baker is directed to numerous secreted and transmembrane polypeptides and the polynucleotides encoding these polypeptides. Although Baker discloses a polypeptide sequence, SEQ ID NO: 400,[2] that allegedly encompasses SEQ ID NO: 3, SEQ ID NO: 400 is not encompassed by the present claims. SEQ ID NO: 400 is a full-length Nogo receptor-1 polypeptide. As clearly defined in the specification as filed, soluble Nogo receptor-1 polypeptides lack the signal sequence and a functional GPI anchor of the full-

[2] The Examiner erroneously refers to SEQ ID NO: 400 as PRO337 in section 17 of the Office Action; however, according to Baker , SEQ ID NO: 400 is PRO526. *See, e.g.*, Baker at column 116, lines 35-41. According to Baker, PRO526 has different properties than PRO337, but regardless, SEQ ID NO: 400 does not meet the limitations of the claims.

length Nogo receptor-1 protein, indicating that the soluble Nogo receptor-1 polypeptides lack the functionality of these domains, in particular, attachment to a cellular membrane through a functional GPI anchor. *See* specification at page 8, lines 4-6. Thus, a sequence comprising the full-length protein cannot inherently have the polypeptide functionality and activity of the soluble Nogo receptor-1 polypeptides of claim 42, because, *inter alia*, SEQ ID NO: 400 would attach to a cellular membrane and, therefore, not be soluble. In addition, the full-length Nogo receptor-1 protein, containing a functional GPI anchor, would function to enhance the production of Aβ peptide, instead of reducing the levels of Aβ peptide as recited in the claim. *See, e.g.*, specification at page 20, line 16, through page 21, line 2.

Moreover, Baker does not disclose a *soluble* Nogo receptor-1 polypeptide by allegedly teaching that the route of administration of PRO polypeptides can be by injection or infusion. A polypeptide solubilized for administration by injection or infusion is not soluble as understood in the context of the soluble Nogo receptor-1 polypeptides of the invention. A soluble Nogo receptor-1 polypeptide is one that lacks an attachment to a cellular membrane, for example, through removal of a functional GPI anchor. A polypeptide solubilized for purposes of administration by injection or infusion is one that has been dissolved in a solvent to form a solution. *See, e.g.*, Theodore Sokoloski, *Solutions and Phase Equilibria, in* REMINGTON'S PHARMACEUTICAL SCIENCES, 207-221 (18th ed. 1990). Although a soluble Nogo receptor-1 polypeptide can be solubilized for administration by injection or infusion, Baker does not disclose or teach a Nogo receptor-1 polypeptide free from attachment to a cellular membrane by allegedly teaching solubilization for purposes of administration by injection or infusion.

The two uses of the term soluble are incongruous. Therefore, Baker does not meet the soluble polypeptide limitation of claim 42.

Thus, Baker does not disclose every element in the claims as currently presented, because the reference does not disclose a soluble Nogo receptor-1 polypeptide that comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain. Accordingly, under *Kalman*, Baker cannot and does not anticipate the claims as currently presented, because this reference fails to disclose each and every limitation recited in the present claims. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(e) therefore are respectfully requested.

B. The Rejection over Baker et al. (U.S. Pat. No. 7,029,874) under 35 U.S.C. § 102(a)

In section 21 of the Office Action at pages 12-14, claims 42, 47, 49, and 58 were rejected as allegedly being anticipated under 35 U.S.C. § 102(a) by Baker. Applicants respectfully traverse this rejection.

As noted above, claim 42 (and thus claims depending therefrom) is drawn to a method for reducing the levels of Aβ peptide in a mammalian brain, comprising administering a therapeutically effective amount of a soluble Nogo receptor-1 polypeptide, wherein said soluble Nogo receptor-1 polypeptide comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain. These methods are not disclosed by Baker.

Applicants reiterate and incorporate by reference herein the remarks made above with respect to Baker. Accordingly, under *Kalman*, Baker cannot and does not anticipate the claims as currently presented, because this reference fails to disclose each and every

limitation recited in the present claims. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(a) therefore are respectfully requested.

C. The Rejection over Eisenbach-Schwartz et al. (U.S. Pub. No. 2002/0072493 A1)

In section 26 of the Office Action at pages 15-16, claims 1-3 were rejected as allegedly being anticipated under 35 U.S.C. § 102(b) by Eisenbach-Schwartz *et al.* (U.S. Pat. Pub. No. 2002/0072493 A1) (hereinafter "Eisenbach-Schwartz"). Applicants would like to point out that claims 1-3 were cancelled in advance of prosecution by a Preliminary Amendment dated August 9, 2006. However, in the event that the Examiner misquoted currently pending claims 42-44 for claims 1-3, Applicants respectfully traverse this rejection with respect to claims 42-44.

As noted above, under 35 U.S.C. §102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman*. As presented, claim 42 (and thus claims depending therefrom) is drawn to a method for reducing the levels of Aβ peptide in a mammalian brain, comprising administering a therapeutically effective amount of a soluble Nogo receptor-1 polypeptide, wherein said soluble Nogo receptor-1 polypeptide comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain. These methods are not disclosed by Eisenbach-Schwartz.

Eisenbach-Schwartz is broadly directed to methods for the promotion of nerve regeneration or to confer neuroprotection and prevent or inhibit neuronal degeneration within the nervous system ("NS") using activated T cells and NS-specific antigens. Although, Eisenbach-Schwartz teaches peptides of NS-specific antigens, including Nogo

receptor, the reference does not disclose soluble Nogo receptor-1 polypeptides because the peptides disclosed, *see, e.g.*, page 9, paragraphs [0110-0112], do not contain an NT domain, eight leucine-rich repeats, and an LRRCT domain, as required by the present claims.

Thus, Eisenbach-Schwartz does not disclose every element in the claims as currently presented, because the reference does not disclose a soluble Nogo receptor-1 polypeptide that comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain. Accordingly, under *Kalman*, Eisenbach-Schwartz cannot and does not anticipate the claims as currently presented, because this reference fails to disclose each and every limitation recited in the present claims. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) therefore are respectfully requested.

V. Request for Interview

Applicants have submitted a PTOL-413A form to request an interview before the issuance of a first Office Action on the merits after the filing of a Request for Continued Examination. As required in the interview request form, Applicants have indicated a time and date for the interview. If this time is not convenient for the Examiner, the Examiner is requested to contact the undersigned attorney and reschedule the interview for a mutually convenient time.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the

Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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